Please add the following claims:

--28. A transgenic non-human mammal or progeny thereof whose somatic and germline cells contain, in stably integrated form,

(a) a first coding sequence encoding an enzymatically active matrix-degrading enzyme (MDE) that degrades an extracellular matrix component, wherein expression of the first coding sequence is under control of a regulatable promoter that is responsive to a transcriptional repressor or activator polypeptide; and

(b) a second coding sequence encoding the transcriptional repressor or activator polypeptide, wherein expression of the second coding sequence is under control of a chondrocyte tissue-specific promoter;

wherein expression of the MDE by chondrocytes is repressed throughout embryonic, fetal, and early postnatal development, and activation of expression of the MDE results in a phenotypic change characteristic of osteoarthritis.

29. The transgenic mammal of claim 28, wherein the MDE is a matrix metalloproteinase selected from the group consisting of MMP-1, MMP-3, MMP-8, and MMP-13.

30. The transgenic mammal of claim 28, wherein the MDE is constitutively enzymatically active without proteolytic processing.

31. The transgenic mammal of claim 30, wherein the MDE is a constitutively enzymatically active MMP-13 variant.

32. The transgenic mammal of claim 31, wherein the MMP-13 variant has a sequence of ID NO:1 or SEQ ID NO:21.

33. The transgenic mammal of claim 28, wherein the mammal is selected from the group consisting of a mouse, a rat, and a rabbit.

34. The transgenic mammal of claim 28, wherein the mammal is a mouse.

35. The transgenic mammal of claim 28, wherein the transcriptional repressor or activator polypeptide is a repressor polypeptide.

36. The transgenic mammal of claim 35, wherein the repressor polypeptide is a tetracycline repressor polypeptide.

37. The transgenic mammal of claim 36, wherein the regulatable promoter comprises a tet07 sequence

38. The transgenic mammal of claim 37, wherein the regulatable promoter comprises a sequence depicted in SEQ ID NO:2.

39. The transgenic mammal of claim 28, wherein the chondrocyte tissue-specific promoter comprises sequences from a Type II collagen promoter.

40. The transgenic mammal of claim 28, wherein the phenotypic change characteristic of osteoarthritis is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen, gross observations of changes in joint function, joint space narrowing, collagen degradation, destruction of cartilage, changes in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof.

41. A transgenic mouse or rat, or progeny thereof, whose somatic and germline cells contain, in stably integrated form,

(a) a first coding sequence encoding a constitutively enzymatically active matrix metalloproteinase (MMP) that cleaves Type II collagen, wherein expression of the first coding sequence is under control of a tetracycline-regulatable promoter; and

(b) a second coding sequence encoding a tetracycline repressor polypeptide that binds to the tetracycline-regulatable promoter, wherein expression of the second coding sequence is under control of a chondrocyte tissue-specific promoter;

wherein expression of the MMP by chondrocytes is repressed throughout embryonic, fetal, and early postnatal development, and activation of expression of the MMP results in a phenotypic change characteristic of osteoarthritis in the transgenic mouse or rat.

42. The transgenic mouse or rat of claim 41, wherein the MMP is constitutively enzymatically active MMP-13, the tetracycline regulatable promoter is a tet07 promoter, the tetracycline repressor polypeptide is a tTA polypeptide, and the chondrocyte tissue-specific promoter comprises sequences from a Type II collagen promoter.

43. The transgenic mouse or rat of claim 42, wherein the phenotypic change characteristic of osteoarthritis is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen, gross observations of changes in joint function, joint space narrowing, collagen degradation, destruction of cartilage, changes in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof.

44. A method for producing a phenotypic change characteristic of osteoarthritis in a transgenic mammal of claim 28, which method comprises activating MDE expression in the transgenic mammal after embryonic, fetal, and early postnatal development.

45. The method according to claim 44, wherein the phenotypic change

characteristic of osteoarthritis is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen, gross observations of changes in joint function, joint space narrowing, collagen degradation, destruction of cartilage, changes in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof.

46. A method for producing a phenotypic change characteristic of osteoarthritis in the transgenic mammal of claim 36, which method comprises maintaining the transgenic mammal on tetracycline or a tetracycline analog during embryonic, fetal, and early postnatal development, and activating the MDE expression by withholding the tetracycline or tetracycline analog after embryonic, fetal, and early postnatal development.

47. The method according to claim 46, wherein the tetracycline analog is doxycycline.

48. The method according to claim 46, wherein the phenotypic change characteristic of osteoarthritis is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen, gross observations of changes in joint function, joint space narrowing, collagen degradation, destruction of cartilage, changes in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof.

49. A method for producing a phenotypic change characteristic of osteoarthritis in the transgenic mouse or rat of claim 41, which method comprises maintaining the transgenic mouse or rat on tetracycline or a tetracycline analog during embryonic, fetal, and early postnatal development, and activating the collagenase expression by withholding the tetracycline or tetracycline analog after embryonic, fetal, and early postnatal development.

50. The method according to claim 49, wherein the tetracycline analog is doxycycline.

51. The method according to claim 49, wherein the phenotypic change characteristic of osteoarthritis is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen, gross observations of changes in joint function, joint space narrowing, collagen degradation, destruction of cartilage, changes in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof.

52. A method for evaluating potential of a composition to counteract a phenotypic change characteristic of osteoarthritis, which method comprises:

(a) administering the composition to the transgenic mammal of claim 28 in which a phenotypic change characteristic of osteoarthritis has been produced by activation of expression of the MDE after embryonic, fetal, and early postnatal development of the transgenic mammal;

(b) monitoring the phenotypic change; and

(c) comparing the extent of the phenotypic change in the mammal to which the composition was administered relative to a control mammal in which expression of the MDE was activated without administering the composition,

wherein any difference in the nature or extent of the phenotypic change, or any difference in the time required for the phenotypic change to develop, indicates the potential of the composition to counteract the phenotypic characteristic of osteoarthritis.

53. A method for evaluating potential of a composition to counteract a phenotypic characteristic of osteoarthritis, which method comprises:

(a) administering the composition to the transgenic mammal of claim 36 in which a phenotypic change characteristic of osteoarthritis has been produced by activating expression of the MDE by withholding tetracycline or a tetracycline analog after embryonic, fetal, and early postnatal development of the transgenic mammal;

(b) monitoring the phenotypic change; and

(c) comparing the extent of the phenotypic change in the mammal to which the composition was administered relative to a control mammal in which expression of the MDE was activated without administering the composition,

wherein any difference in the nature or extent of the phenotypic change, or any difference in the time required for the phenotypic change to develop, indicates the potential of the composition to counteract the phenotypic characteristic of osteoarthritis.

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54. A method for evaluating potential of a composition to counteract a phenotypic change characteristic of osteoarthritis, which method comprises:

(a) administering the composition to the transgenic mouse or rat of claim 41 in which a phenotypic change characteristic of osteoarthritis has been produced by activating expression of the MMP by withholding tetracycline or a tetracycline analog after embryonic, fetal, and early postnatal development of the transgenic mouse;

(b) monitoring the phenotypic change; and

(c) comparing the extent of the phenotypic change in the mouse or rat to which the composition was administered relative to a control mouse or rat in which expression of the MMP was activated without administering the composition,

wherein any difference in the nature or extent of the phenotypic change, or any difference in the time required for the phenotypic change to develop, indicates the potential of the composition to counteract the phenotypic characteristic of osteoarthritis.--

REMARKS

This Application is a Continuation of Serial No. 08/994,689 (the '689 application), which has been finally rejected in an Office Action dated September 29, 2000. The claims in this preliminary rejection are substantively identical to the claims finally rejected in the '689 application. Some changes to address clarity rejections have been made to the claims.